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Gut-microbiota-brain axis and effect on neuropsychiatric disorders with suspected immune dysregulation

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Abstract

Purpose—Gut microbiota regulate intestinal function and health. However, mounting evidence indicates that they can also influence the immune and nervous systems and vice versa. Here we reviewed the bidirectional relationship between the gut microbiota and the brain, termed microbiota-gut-brain (MGB) axis, and we discuss how it contributes to the pathogenesis of certain disorders, that may involve brain inflammation.

Methods—Articles were chosen from Medline since 1980 using the key words anxiety, attention-deficit hypersensitivity disorder (ADHD), autism, cytokines, depression, gut, hypothalamic-pituitary-adrenal (HPA) axis, inflammation, immune system, microbiota, nervous system, neurologic, neurotransmitters, neuroimmune conditions, psychiatric, stress.

Findings—Various afferent or efferent pathways are involved in the MGB axis. Antibiotics, environmental and infectious agents, intestinal neurotransmitters/neuromodulators, sensory vagal fibers, cytokines, essential metabolites, all convey information about the intestinal state to the CNS. Conversely, the HPA axis, the CNS regulatory areas of satiety and neuropeptides released from sensory nerve fibers affect the gut microbiota composition directly or through nutrient

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Disclosures

TCT is the inventor of US patents No. 6,624,148; 6,689,748; 6,984,667, and EPO 1365777, which cover methods and compositions of mast cell blockers, including flavonoids, as well as US patents No 7,906,153 and 8,268,365 for treatment of brain inflammation.

Conflicts of interests

The authors declare no conflicts.

availability. Such interactions appear to influence the pathogenesis of a number of disorders in which inflammation is implicated such as mood disorder, autism-spectrum disorders (ASDs), attention-deficit hypersensitivity disorder (ADHD), multiple sclerosis (MS) and obesity.

Implications—Recognition of the relationship between the MGB axis and the neuroimmune systems provides a novel approach for better understanding and management of these disorders. Appropriate preventive measures early in life or corrective measures such as use of psychobiotics, fecal microbiota transplantation and flavonoids are discussed.

Keywords

gut; microbiota; immune disorders; nervous system diseases; MGB axis; cytokines

Introduction

Humans have up to 37% gene homology with Bacteria and Archae[1]. Great numbers of commensal microorganisms reside on both the external and the internal surfaces of our bodies, especially the gut, outnumbering human somatic cells by approximately 10:1[2]. Our colonization starts at birth during vaginal delivery with a maternal signature followed by complex "adult" microbiota after the first year of age[3, 4]. As a result, the human body is considered as a super-complex ecosystem, a social network with the gut microbiota having formed a permanent symbiotic relationship rather than a temporary form of parasitism[5]. Normally, the gastrointestinal (GI) microbiota has a symbiotic relationship with our enteric cells and contributes to basic physiological processes including digestion, growth and self-defense (Table 1).

An individual's gut microbiota composition depends on the mode of delivery at birth, genetic predisposition, age, nutrition, physical activity, environmental factors, stress, infections, other diseases and use of antibiotics. Brain function and psychological make-up are now increasingly considered to have a reciprocal relationship with the gut[6].

Disruption of the gut microbiota (dysbiosis) balance is known to contribute, among others, to the pathogenesis of GI diseases, especially inflammatory bowel disorder (IBD)[7] and irritable bowel syndrome (IBS)[8], especially since the gut microbiome regulates immunity[9–13]. In fact, bacteria reported to directly induce inflammation and pain[14]

Accumulating evidence suggests that the gut microbiota maintain bidirectional interactions with critical parts of the central nervous system (CNS) and the immune system through direct and indirect pathways (Table 2 and Fig. 1). These involve the endocrine [hypothalamic-pituitary-adrenal (HPA) axis], immune (chemokines, cytokines), autonomic nervous system (ANS) and enteric nervous systems forming the microbiota-gut-brain (MGB) axis[6].

Neuro/immune-active substances derived from the intestinal lumen can penetrate the gut mucosa, be transported by blood, cross the blood-brain-barrier (BBB) and affect the CNS[15]. Gut microbiota can influence CNS function through their ability to synthesize or mimic a range of host-signaling neuroactive molecules, such as acetylcholine (Ach), catecholamines, gamma-aminobutyric acid (GABA), histamine, melatonin and 5-hydroxytryptamine (5-HT, serotonin)[16]. 5-HT is crucial in the regulation of peristalsis or modulation of sensation[17].

Conversely the composition of gut microbiota is influenced by emotional and physiological stress[18]. One study found that healthy students during an extremely stressful time had fewer *Lactobacilli* present in their stool as compared to less stressful periods[19]. Maternal separation stress between 6–9 months of age in rhesus monkeys resulted in decreased faecal *Lactobacilli*[20]. Exposure to chronic stress in adult mice decreased the relative abundance of *Bacteroides* species and increased the *Clostridium species* in the caecum; moreover, it caused activation of the immune system as documented by increased IL-6 and CCL2 production[21]. Acute stress increased GI[22, 23] and BBB[24] permeability through activation of mast cells (MCs), which express high affinity receptors for CRH[25]. Moreover, chronic stress disrupted the intestinal barrier through MC activation and permitted penetration of luminal antigens, microflora metabolites, toxins and lipopolysaccharide (LPS) into the systemic circulation and the CNS[26]. In fact, stress-induced MC activation has been implicated in functional GI diseases[27]. Maternal separation stress in mice also increased intestinal MC-neuron communication[28].

MCs communicate with pathogens[29] and have been invoked as key modulatory cells in innate immunity[30], as well as in inflammation[31–34] and autoimmunity[35]. A new finding concerning MCs is their ability to secrete mitochondrial components, including DNA, extracellularly[36]. These components are then misconstrued by the body as “innate pathogens” and induce a strong auto-inflammatory response[36] leading to inflammation and neuronal damage[37]. The microbiota can also modulate the immune system through other mechanisms[38] And the increased use of antibiotics results in depletion of microbiota-derived metabolites, impairs immune homeostasis and contributes to chronic inflammation[39].

Mood disorders

Genes involved in synapse formation between neurons in the brain and neurons in the GI tract are quite similar, and any mutations could possibly lead to both brain and GI abnormalities[40]. Recent studies analyzing the human genome in brains from diseased individuals with psychiatric disorders reported only two clusters of affected genes with: (a) increased inflammation and (b) decreased mitochondrial function[41]. Depression is associated with increased inflammatory biomarkers, such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and C reactive protein (CRP)[42]. Schizophrenia has been linked to intestinal inflammation[43] and gastrojejunal ulcers[44].

“Psychobiotics”, which are live organisms, when ingested may produce health benefits in patients suffering from mood disorders[45]. In a study of 124 healthy volunteers (mean age 61.8 years), those who consumed a mix of specific psychobiotics *(Lactobacillus helveticus and bifidobacterium longum)* exhibited less anxiety and depression[19]. Symptoms of “depression” were reported to decrease following probiotic treatment in the rat[46]. Additional studies showed beneficial effects of probiotics in animal models with altered behavioral phenotypes, as they reduced vagal-dependent activation of GABA receptors in response to physical and psychological stress[46–51].

Studies in animals showed that certain bacterial species could reduce mood changes. For inastance, when *Citrobacter rodentium* was administrated orally to CF-1 mice, there was an increase in anxious-like behavior 7–8 hours following the infection, through activation of vagal pathways[52]. Postnatal colonization of germ-free (GF) mice by orally feeding them with different probiotics programmed the HPA for a stress response; for instance, when *Campylobacter jejuni* was given orally, it increased anxious-like behavior 7 hours after the infection[53]. Furthermore, a corresponding increase in brain-derived neurotrophic factor (BDNF) in the hippocampus and amygdala was evident and was eliminated after administration of antibiotic therapy in the mice[53]. Of note, BDNF is involved in the pathology of depression[54] and Autism Spectrum Disorders (ASDs)[55], while it is also considered a biomarker for gastric hypersensitivity[56].

Attention-Deficit Hypersensitivity Disorder (ADHD) and Autism Spectrum Disorders (ASDs)

ADHD is a neurodevelopmental disorder characterized by lack of attention, impulsiveness and hyperactivity. Its cause is considered multifactorial, involving genetic pre-disposition, somatic mutations, epigenetic changes, perinatal factors (e.g. low birth weight, prematurity and prenatal exposure to alcohol and/or smoke), as well as environmental and socioeconomic factors[57].

Increasing evidence from clinical and epidemiological studies suggests that children and adults with food allergies, eczema or asthma are associated with behavioral problems and neuropsychiatric disorders, including ADHD[58–63]. The gut microbiota are known to participate in susceptibility to allergies[64, 65], especially food allergens[66].

One meta-analysis reported that the Kaiser-Permanente (K-P) diet using elimination of salicylates, artificial food colors (AFC) and flavors, as well as the preservative butylated hydroxytoluene, could decrease the hyperactivity of ADHD children[57]. Children with ADHD were substantially improved on either an AFC-free diet[67], or by dietary supplementations with polyunsaturated fatty acids (PUFA), iron and zinc[68]. In fact, PUFA levels in plasma of ADHD children were reported low[69]. Food-based treatments in children with allergic disorders significantly reduced ADHD-like behavior[70].

Autism spectrum disorders (ASDs) are neurodevelopmental disorders characterized by deficits in social interactions and communication, along with repetitive and stereotyped behaviors[71].

Many children with ASDs present with GI symptoms[72–74] and altered GI flora[71]. Increasing evidence indicates that ASD pathogenesis may involve brain inflammation[75] especially activation of microglia[76, 77]. Moreover, about 30% of children with ASDs have auto-antibodies against brain proteins[78] and the presence of such antibodies strongly correlated with allergic symptoms[79].

We recently showed that levels of the neuropeptide neurotensin (NT), found both in the brain and the gut and CRH were increased in the serum of children with ASDs; moreover, NT was significantly correlated with the presence of GI symptoms[80]. We also reported elevated levels of mitochondrial DNA in the serum of children with ASDs[81] and CRH augmented the stimulatory effect of mitochondrial DNA on MCs[82]. A paper recently reported increased amount of mitochondrial DNA in peripheral mononuclear cells (PBMC) from patients with ASDs[83]. Extracellular mitochondrial DNA could derive either from MCs, PBMC, intestinal cells or bacteria and is misconstrued as “innate pathogens” leading to auto-inflammatory reactions[84].

About 30% of ASD children are characterized by hyperserotonemia[85] and a serotonin re-uptake transporter (SERT) gene mutation *(SERT Ala56)* was identified in some ASD children with hyperserotenemia[86]. Introduction of this mutation in mice resulted in communication delays and repetitive behaviors similar to those in children with ASDs[86]. In fact, 5-HT can affect the immune system[28], and autoimmune neuroinflammation was treated with a tryptophan metabolite[87].

The *SERT Ala56* mice were also constipated and had bacterial intestinal overgrowth similar to what is often seen in children with ASDs[88].

Increased intestinal permeability would permit bacterial products, cytokines and chemokines to enter the circulation and cross the BBB[89] influencing brain and behavior. For example, children with ASDs had higher levels of immunoglobulins (IgA, IgG, IgM) against cow’s milk-derived allergens, and milk intake by these patients significantly worsened some of their behavioral symptoms[70]. Elimination of caseinomorphin, gliadomorphin, colorings, sweeteners and preservatives led to significant benefit[70]. The gut microbiota composition appears to differ between healthy children and those with ASDs[71]. For example, there was a higher prevalence of *Bifidobacteria* in healthy controls as compared to ASD patients[90]. In contrast, *Bacteroides vulgatus* and *Desulfovibrio species* were more commonly found in stools of ASDs children; however, only *D. desulfuricans, D. fairfielddensis* and *D. piger* were associated with regressive ASD. *Clostridium* species were increased at the expense of *Bifidobacterium* in ASD children with food allergies and pediatric IBD as compared to sex-matched controls children[91]. ASD children treated with oral vancomycin had significant improvement in behavioral, cognitive and GI symptoms[92]. Such findings are discussed in detail in another manuscript in this issue.

Such findings have led to the gut-to-brain connections being proposed as target for treatment of ASDs[93].

Multiple Sclerosis (MS) and Neuromyelitis optica (NMO)

Multiple sclerosis (MS), an autoimmune disease characterized by progressive demyelination and deterioration of neurological function[94, 95]. It has been suggested that gut microbiota may contribute to the pathogenesis of MS[96]. One study showed that germ-free mice had delayed induction of experimental autoimmune encephalomyelitis (EAE), probably due to the attenuation of Th17 and auto-reactive B cell responses[96]. In another study, mice genetically predisposed to develop EAE spontaneously did not develop EAE when housed under germ-free conditions; however, this was reversed upon colonization with conventional microbiota in adulthood[97]. Even the presence of commensal microbiota promoted the induction of EAE in germ-free B6 mice due to decreased IFN-γ and IL-17 responses[98].

High-fat diet was found to increase EAE severity in mice, while caloric restriction attenuated EAE symptoms[99].

Patients with NMO have aquaporin (AQP) autoantibodies (AQP4-seropositive) against the optic nerve and spinal cord, but also more antibodies against GI antigens than healthy controls[100]. Specifically, 37% of these patients had increased levels of antibodies at least against one of the following: gliadin, tissue transglutaminase (tTG), intrinsic factor (IF), parietal cells (PC) and *Saccharomyces cerevisiae* compared to 8% of healthy controls, with anti-gliadin and ASCA being the most frequent in AQP4-seropositive NMO (P=0.01 and P<0.05, respectively[100]. In addition, the AQP4-specific T-cells in NMO patients showed cross-reactivity to a protein of *Clostridium perfrigens*, supporting a microbiota-related molecular mimicry process in NMO pathogenesis[101]. MS[102] and EAE[103] are precipitated or worsen by stress, which is known to also affect the gut[104]. In fact, stress-induced gut alterations can impact the brain and behavior[105].

5. Obesity

Obesity has been called a psychiatric disease[106] and is associated with depression[107] and other neuropsychiatric disorders[43]Adipocytokines can influence both the brain and the gut[106]. Recent evidence suggests that gut microbiota influence energy balance and weight[68]. Increased energy harvesting from diet, regulation of biologically active fatty acid tissue composition, chronic low-grade endotoxemia and modulation of gut-derived peptide secretion are some of the proposed routes that link gut microbiota with obesity[108].

Gut microbiota may also contribute to low-grade inflammation in obesity[109]. Increased fat intake has been associated with increased serum levels of LPS in normal humans[110] and mice[111]. This endotoxin can potentially trigger toll-like receptors (TLRs) in adipose or on pancreatic β-cells, contributing to both insulin resistance and β-cell damage[112, 113]. Experimental endotoxemia induced adipose inflammation and insulin resistance in lean human subjects[114]. Modulation of gut microbiota by using probiotics in obese mice was found to decrease high-fat-diet-induced LPS endotoxemia, as well as systemic and liver inflammation[111, 112].

There are many studies with contradictory results concerning the types of bacteria that predominate in obese as compared to lean individuals[115–117]. For instance, metabolically obese mice with mutated leptin gene had different microbiota than mice without the mutation[115]. The same researchers later reported altered gut microbiota composition (reduction of *Bacteroidetes* and increase of *Firmicute phyla*) in obese human subjects compared to lean human subjects[118]. In contrast, other authors reported higher proportion of *Bacteroidetes* in overweight and obese subjects[119]. These conflicting results may be due to the variable methods of analysis and to the different profile of subjects.

Gut microbiota can convert undigested carbohydrates into short-chain-fatty acids (SCFA), like acetate, propionate and butyrate. These SCFAs are able to bind and activate two G-protein-coupled receptors (GPR41 and GPR43) on gut epithelial cells, leading to secretion of petide YY (PYY), which suppresses gut motility and retards intestinal transit[108]. It is interesting that propionate could induce an autistic-like phenotype in rats[120].

Modulation of gut microbiota may have therapeutic potential in the management of metabolic disorders[121].

Treatment and Future Directions

Therapeutic modulation of gut microbiota possibly by the use of pPre- and probiotics may be helpful in disorders involving MGB axis disturbances[122]. Prebiotics can benefit both intestinal mucosa and systemic immunity as they reach the large intestine non-hydrolyzed and stimulate the growth of beneficial intestinal microbiota[123]. Probiotics could restore intestinal permeability by improving mucosal barrier function[124]. Administration of different probiotics has been reported to be beneficial in humans with abdominal pain[125, 126] and increased the pain threshold in rats[127]. *Lactobacillus acidophilus* induced the expression of the cannabinoid 2 and μ-opioid 1 receptors in the colonic epithelium[128], while *Lactobacillus farciminis* inhibited stress-induced visceral hypersensitivity[129]. However, use of probiotics may result in both beneficial and detrimental effects. For example, there were beneficial effects in IBS with the use of probiotics *Bifidobacterium infantis 35624*[130, 131] and *Bifidobacterium lactis and animalis DN173010*[132] and of probiotic mixtures, such as *Escherichia coli (DSM 17252)* and *Enterococcus faecalis (DSM 16440)*[133] or *Lactobacillus rhamnosus GG, L. rhamnosus LC705, Bifidobacterium breve Bb99* and *Propionibacterium freudenreichii ssp. shermanii JS*[134, 135]. On the contrary, use of other probiotic mixtures, such as *Lactobacillus paracasei spp. Paracasei F19, L. acidophilus La5 and Bifidobacterium lactis Bb12*[136, 137] or *Lactobacillus plantarum MF1298*[138] had negative effects in IBS. Non-absorbable antibiotics (e.g. oral rifaximin) was shown to be beneficial in IBS[139].

Natural flavonoids may be useful because they have immunoregulatory actions[140]. For instance, the quercetin glycoside rutin is cleaved by gut bacteria to liberate quercetin, which has anti-inflammatory actions[141]. Both quercetin, luteolin and tetramethoxyluteolin are potent inhibitors of MCs[142].

Fecal microbiota transplantation (FMT) from a healthy donor can re-establish intestinal flora balance and could be used for specific GI diseaseS[143], especially the treatment of *Clostridium difficile* infection[144] and possibly be efficacious in IBD[145].

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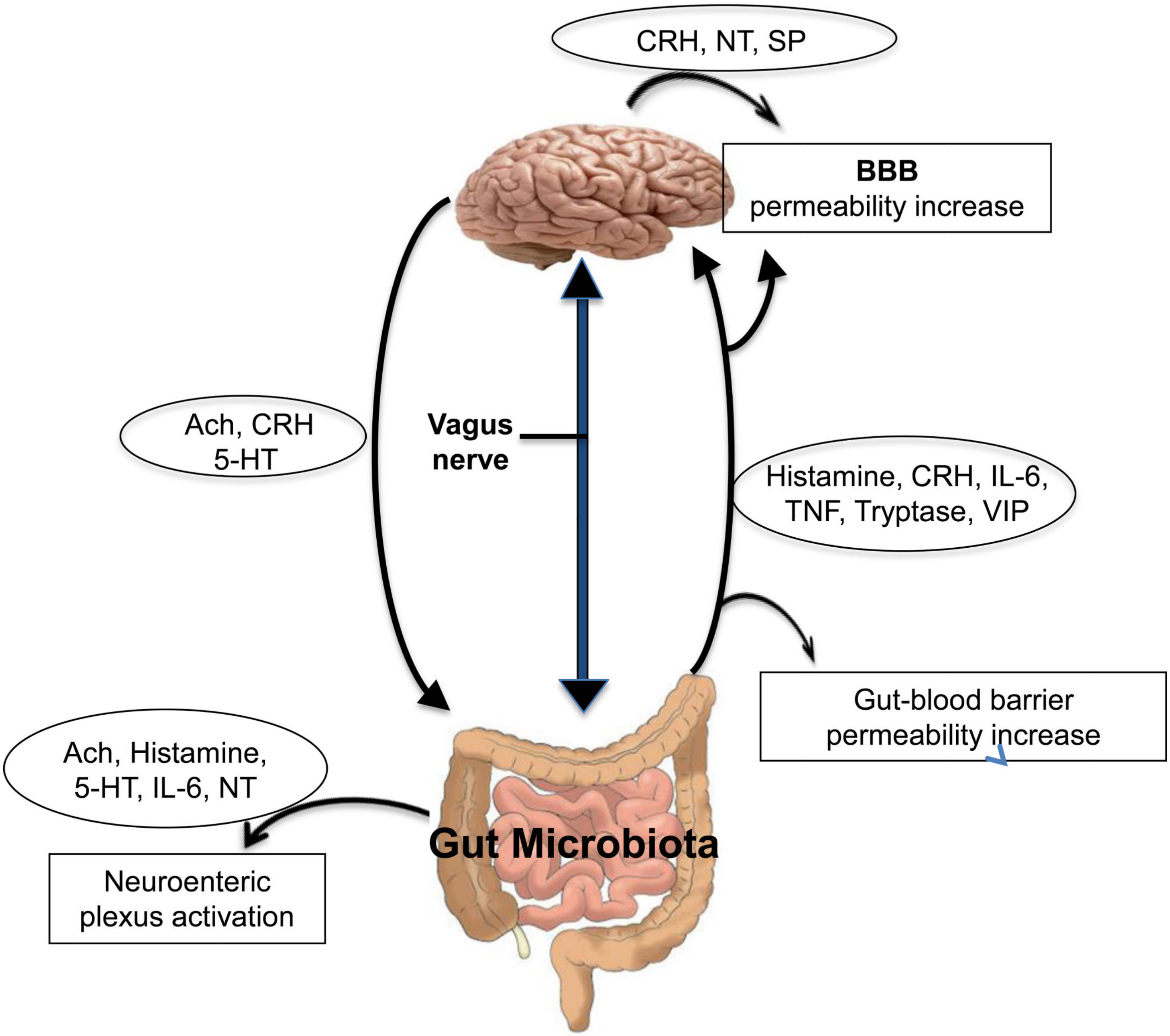

Figure 1. Diagrammatic representation of the M-G-B axis showing the proposed bidirectional communications

Gut microbiota can release molecules that can: activate the neuroenteric plexus, stimulate brain production of neuropeptides, as well as increase gut-blood barrier and BBB permeability. The brain releases molecules that stimulate the neuroenteric plexus and gut function. The vagus nerve sends orthodromic and antidromic.

Ach= Acetylcholine

BBB= Blood-brain barrier

CRH= Corticotropin-releasing hormone

5-HT= 5-hydroxytryptamine

IL-6= Interleukin 6

NT= Neurotensin

SP= Substance P

TNF= Tumor necrosis factor

VIP= Vasoactive intestinal peptide

Table 1

Beneficial Functions of Gut Microbiota

- Defense against pathogen colonization by nutrient competition and production of antimicrobial substances
- Fortification of intestinal epithelial barrier and induction of secretory IgA (sIgA) synthesis to limit pathogenic bacteria penetration into tissues
- Facilitation of nutrient absorption by metabolizing indigestible dietary compounds
- Participation in the maturation and functionality of the host immune system by providing diverse signals for “tuning” the host immune status

Table 2

Pathways Involved in Bidirectional Communication Between Gut Microbiota, the Brain and the Immune System

Afferent arm	
Pathways	***Effect***
Change of the gut microbiota due to usage of antibiotics/ infectious agents/probiotic bacteria	Alteration in the circulating levels of pro/anti-inflammatory cytokines that affect brain function
Modulation of various host metabolic reactions	Production of essential metabolites (bile acids, choline, short-chain fatty acids)
Generation of neurotransmitters or neuromodulators in the intestinal lumen	Induction of epithelial cell release of molecules that stimulate afferent axons
Changes in tryptophan metabolism	Effects on behavior
Activation of sensory vagal fibers	Conveyance of information about the state of intestine to the CNS
Efferent arm	
Pathways	***Effect***
HPA axis activation	Regulation of immune cells locally in the gut and systematically affecting gut permeability, motility, secretion, barrier function and gut microbiota composition
Anti-inflammatory cholinergic reflex and/or sympathetic activation	Release of neurotransmitters that may affect gut microbiota composition, intestinal permeability and local immunity
Activation of CNS regulatory areas of satiety	Impact on nutrient availability to intestinal microbiota and their composition